DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20852
Telephone: 301-435-0062
FAX: 301-402-2071

April 29, 2002

Dr. Fazwaz T. Ulaby
Vice President for Research
University of Michigan Ann Arbor
4080 Fleming Building
503 Thompson Street
Ann Arbor, MI 48109-1340

RE: Human Research Protections Under Multiple Project Assurance (MPA) M-1184

Multistudy Research Project: Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (N.Engl. J Med 2000;342:1302-8)

UM Approved Protocols:

(1) Prospective, Randomized, Multicenter Trial of 12ml/kg vs. 6 ml/kg Tiday Volume Positive Pressure Ventilation and Ketoconazole vs. Placebo for Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome (IRB No. 1996-152)(Galen Toews, P.I.)

(2) Ketoconazole and Respiratory Management in Acute Lung Injury and Adult Respiratory Distress Syndrome (KARMA) (IRB No. 1996-152, Version 2) (Galen Toews, P.I.)

(3) A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Trial of Lisofylline in Patients with Acute Lung Injury and Adult Respiratory Distress Syndrome (IRB No. 1998-081) (Galen Toews, P.I.)

Dear Dr. Ulaby:

The Office for Human Research Protections (OHRP) has reviewed the University of Michigan's (UM's) April 12, 2002 letter regarding the above-referenced research, which was submitted in response to OHRP's February 11, 2002 letter.

Based upon its review, OHRP makes the following determinations regarding the above-referenced research:

(1) In its February 11, 2002 letter, paragraph (3), OHRP found that the informed consent documents for the above research failed to adequately describe all reasonably foreseeable risks and discomforts of receiving non-traditional, 6 ml/kg tidal volume mechanical ventilation, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(2).

Corrective Action: OHRP finds that UM has adequately addressed OHRP's finding. Specifically, OHRP notes that UM has increased the number of IRBs from 1 to 4, primarily to permit more focused IRB review of informed consent documents. In addition, UM IRB's amended Operating Procedures stress the necessity of describing any foreseeable risks or discomforts associated with a protocol, and now clarify an intensified IRB role in reviewing adverse events to determine whether there are risk changes that would make appropriate notification of existing subjects or revision of consent documentation for future subjects. OHRP finds these corrective actions to be satisfactory and appropriate under the UM MPA.

(2) HHS regulations at 45 CFR 46.117(c) permit a waiver of the requirement to obtain a signed consent form for some or all research subjects under certain limited circumstances. In its February 11, 2002 letter OHRP acknowledged UM's plan to develop standards and guidance for obtaining telephonic consent from patient representatives of subjects unable to consent personally that complied with the requirements of 45 CFR 46.117. OHRP requested that UM provide a copy of these standards and guidance to OHRP.

OHRP finds that UM's draft Quick Guide to Waiver of Informed Consent and Use of Telephonic Consent Procedures enclosed with its April 12, 2002 letter complies with the requirements of HHS regulations at 45 CFR 46.117.

(3) HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require that institutions have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, any supporting Department or Agency head, and OHRP of (i) any unanticipated problems involving risks to subjects or others; (ii) any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB; and (iii) any suspension or termination of IRB approval. In its February 11, 2002 letter, OHRP found that UM's reporting policies did not comply with HHS regulatory requirements and required UM to submit a corrective action plan to address this deficiency. OHRP finds that UM's draft reporting policy attached to its April 12, 2002 letter satisfies HHS regulatory requirements at 45 CFR 46.103(a) and 46.103(b)(5).

(4) HHS regulations at 45 CFR 46.111(b) stipulate that in order to approve research, the IRB shall determine that when some or all of the subjects are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of the subjects. In its February 11, 2002 letter, OHRP expressed concern that the UM IRB failed to ensure that this requirement was satisfied for the above-referenced research. OHRP finds that UM has adequately addressed this concern. Furthermore, OHRP acknowledges that the UM IRBs have implemented procedures to ensure consideration of additional safeguards for research involving vulnerable subjects.

UM's April 12, 2002 letter appeared to question the assumption that the family members of ICU patients could likely be vulnerable to coercion or undue influence:

> "We know of no basis, however, for considering the relatives of patients with impaired levels of consciousness to be vulnerable subjects."

OHRP notes that the possibility of coercion or undue influence when obtaining consent from legally authorized representatives, as well as from subjects directly, is expressly contemplated in the human subject protection regulations. HHS regulations at 45 CFR 46.116 obligate investigators to obtain informed consent "only under circumstances that provide the prospective subject *or the representative* sufficient opportunity to consider whether or not to participate *and that minimize the possibility of coercion or undue influence*."

(5) OHRP finds that UM has adequately addressed the additional concerns raised in OHRP's February 11, 2002 letter.

As a result of the above determinations, and assuming full implementation of required actions, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

At this time, OHRP provides the following additional guidance in response to UM's April 12, 2002 letter:

(6) HHS regulations at 45 CFR 46.116(d)(3) for waiving the requirements for obtaining informed consent require that the IRB find and document that the research could not practicably be carried out without the waiver. Please note that mere inconvenience in contacting individuals is not a justification for concluding that obtaining informed consent is impracticable.

OHRP appreciates the commitment of UM to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Carol J. Weil, J.D.
Division of Compliance Oversight

cc: Dr. Galen Toews, UM
Dr. Judity Novack, Assistant Vice President for Research, UM
Dr. David Smith, Chair, IRB-01, UM
Dr. Charles Kowalski, Chair, IRB-02, UM
Dr. Eugene Burnstein, Chair, IRB-03, UM
Dr. Gerald Gardner, Chair, IRB-04, UM
Dr. Suzanne Selig, Chair, IRB-05, UM
Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael Carome, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey Cohen, OHRP
Ms. Janice Walden, OHRP
Mr. Barry Bowman, OHRP
Commissioner, FDA
Dr. David Lepay, FDA
Dr. John Mather, Director, ORCA, Veterans Health Administration